

Safety and efficacy of DYNE-101 in adults with DM1: Phase 1/2 ACHIEVE trial data

Daniel Wolf¹, Guillaume Bassez², Jordi Diaz-Manera³, Joost Kools⁴, James B. Lilleker⁵, Marika Pane⁶, Richard H Roxburgh⁷, Benedikt Schoser⁸, Christopher Turner⁹, Chris Mix¹, Soma Ray¹, Baoguang Han¹, Douglas Kerr¹, Valeria Sansone¹⁰

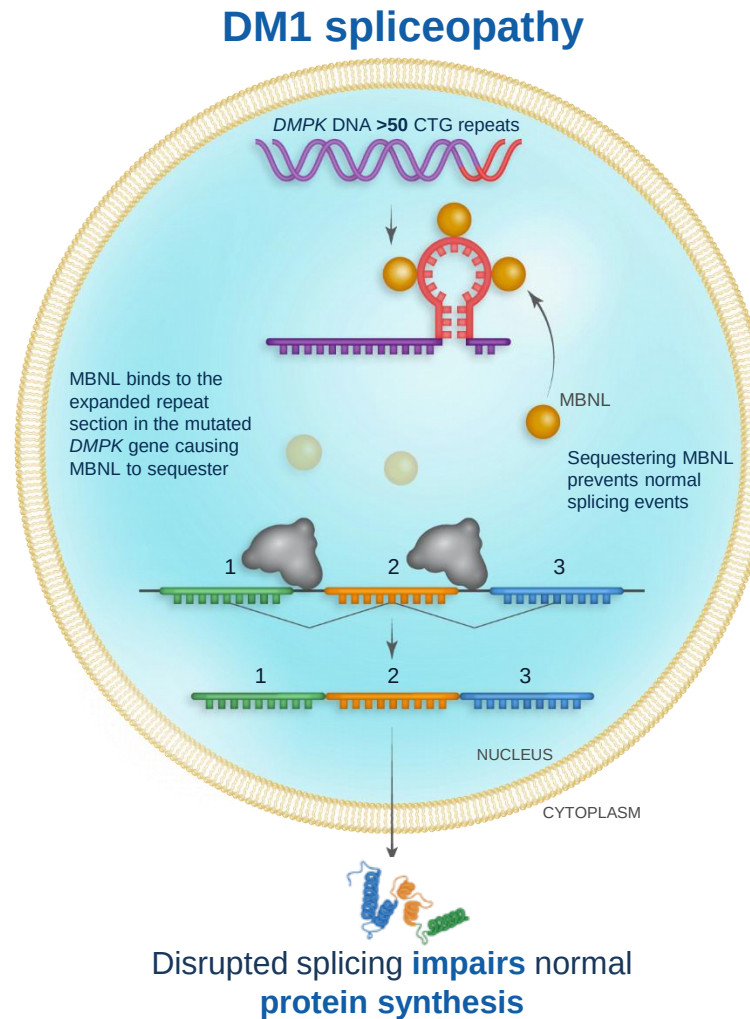
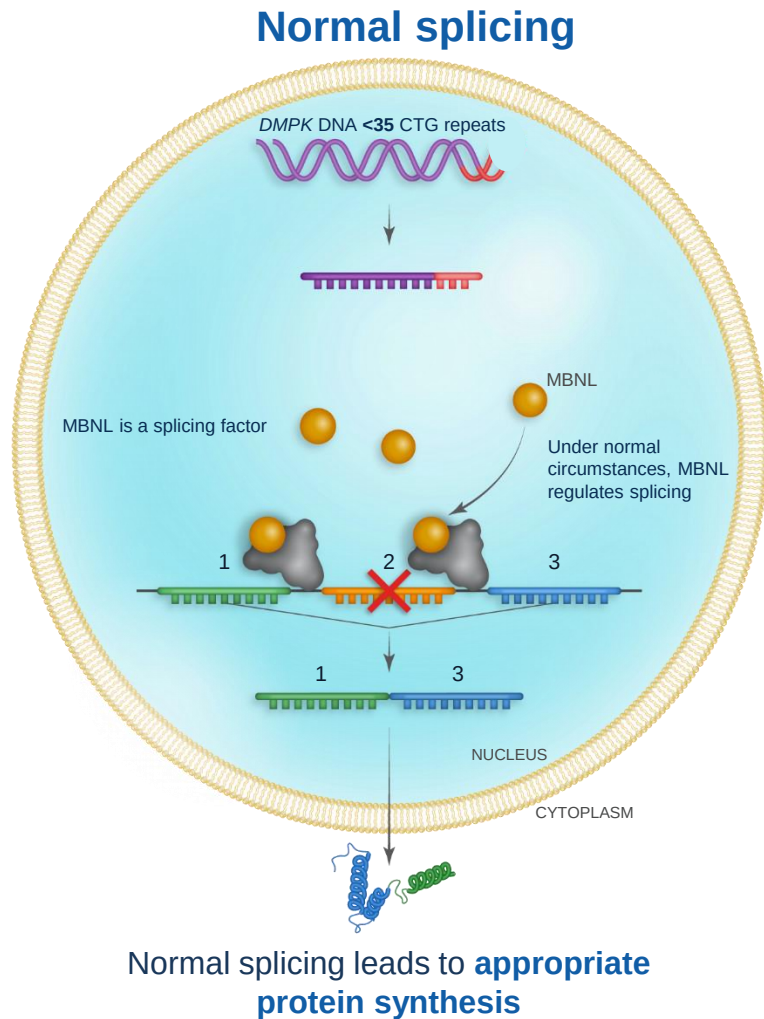
¹Dyne Therapeutics, Inc., Waltham, MA, USA; ²Institut de Myologie, Paris, France; ³John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle-Upon-Tyne, UK; ⁴Radboud University Medical Center, Nijmegen, Netherlands; ⁵Muscle Disease Unit, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; ⁶Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; ⁷Neurogenetics Clinic Centre for Brain Research, University of Auckland, Auckland, NZ; ⁸Friedrich-Baur-Institute, Dep. of Neurology LMU Clinics, Ludwig-Maximilians University, Munich, Germany; ⁹University College London Hospitals, London, UK; ¹⁰Centro Clinico NEMO, University of Milan, Milan, Italy



Disclosures and forward-looking statements

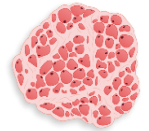
- I am an employee of and may own stocks in Dyne Therapeutics, Inc.
- DYNE-101 is an investigational medicine being evaluated in the ongoing ACHIEVE trial and has not received approval by the FDA, EMA, or any other regulatory authorities
- This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding Dyne's strategy, future operations, prospects and plans, objectives of management, the potential of the FORCE platform, the therapeutic potential of DYNE-101, and enrolling registrational cohorts and initiating additional clinical trials, and plans to provide future updates on pipeline programs, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "objective," "ongoing," "plan," "predict," "project," "potential," "should," or "would," or the negative of these terms, or other comparable terminology are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Dyne may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including: uncertainties inherent in the identification and development of product candidates, including the initiation and completion of preclinical studies and clinical trials; uncertainties as to the availability and timing of results from preclinical studies and clinical trials; the timing of and Dyne's ability to enroll patients in clinical trials; whether results from preclinical studies and data from clinical trials will be predictive of the final results of the clinical trials or other trials; whether data from clinical trials will support submission for regulatory approvals; uncertainties as to the FDA's and other regulatory authorities' interpretation of the data from Dyne's clinical trials and acceptance of Dyne's clinical programs and as to the regulatory approval process for Dyne's product candidates; whether Dyne's cash resources will be sufficient to fund its foreseeable and unforeseeable operating expenses and capital expenditure requirements; as well as the risks and uncertainties identified in Dyne's filings with the Securities and Exchange Commission (SEC), including the Company's most recent Form 10-K and in subsequent filings Dyne may make with the SEC. In addition, the forward-looking statements included in this presentation represent Dyne's views as of the date of this presentation. Dyne anticipates that subsequent events and developments will cause its views to change. However, while Dyne may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing Dyne's views as of any date subsequent to the date of this presentation.

Spliceopathy in DM1 drives multi-system disease manifestations



Consequences of spliceopathy

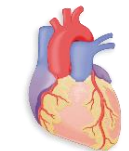
Myotonia and muscle weakness



Cognitive impairment, fatigue, EDS



Cardiac conduction complications



Pulmonary abnormalities



Abnormal splicing in **multiple tissues** causes symptoms of DM1

Goal of treatment: address the genetic cause of DM1 to correct splicing and enable functional improvement

DYNE-101 addresses the central pathobiology of DM1 to enable broad functional improvement

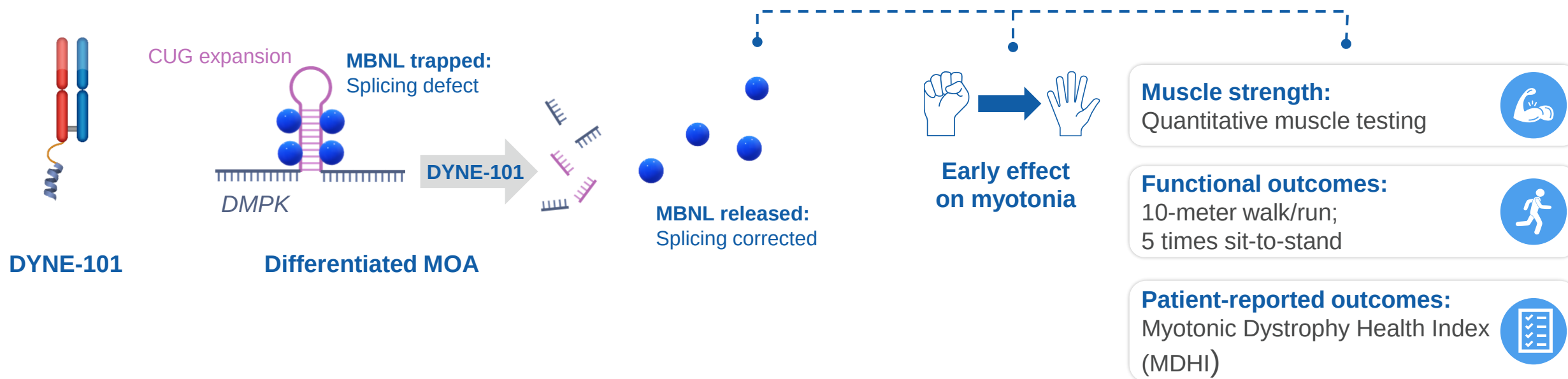
Robust and widespread delivery

DMPK degradation in the nucleus

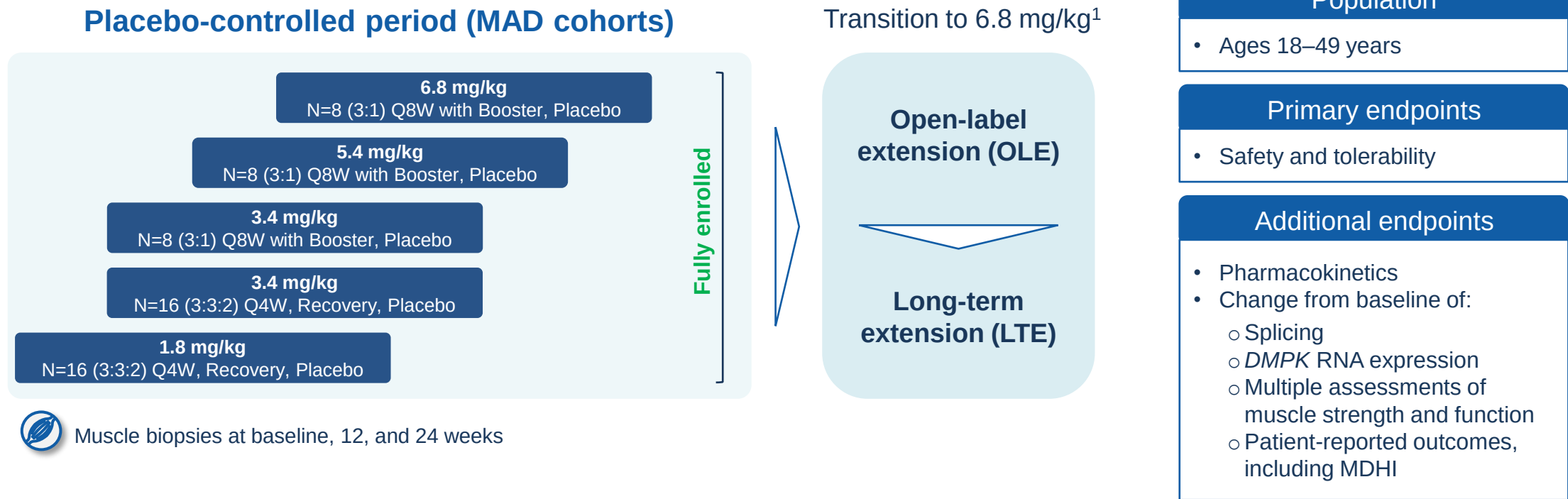
MBNL release and splicing correction

Early clinical effect

Broad functional improvement



ACHIEVE trial of DYNE-101 in adults with DM1



Registrational dose and dose regimen selected at 6.8 mg/kg Q8W; Registrational expansion cohort planned (N=32–48, 3:1 randomization)

Doses provided refer to antisense oligonucleotide component of DYNE-101. Recovery cohort Q4W x 2 doses then placebo for the remainder of the 24W placebo-controlled period. Q8W with booster includes Q4W x 3 doses then Q8W dosing. Additional endpoints include select secondary and exploratory endpoints.

1. Transition to 6.8 mg/kg dose occurs at non-uniform times during OLE or LTE.

DM1, myotonic dystrophy type 1; DMPK, dystrophin myotonia protein kinase; MAD, multiple ascending dose; MDHI, Myotonic Dystrophy Health Index; Q4W, every 4 weeks; Q8W, every 8 weeks.

Baseline participant characteristics in 6.8 mg/kg Q8W cohort

Mean (SD) or n (%)	Placebo (N=14)	6.8 mg/kg Q8W (N=6)
Age (years)	32.6 (9.6)	37.2 (9.7)
BMI (kg/m ²)	24.4 (4.7)	23.4 (5.6)
CASI-22	0.68 (0.20)	0.74 (0.25)
CTG repeats	597 (246)	542 (191)
vHOT (middle finger) (sec)	7.5 (3.0)	7.8 (3.8)
QMT total (% predicted)	51.5 (14.3)	51.3 (10.4)
10-meter walk/run (sec)	3.34 (0.48)	3.94 (1.56)
5 times sit-to-stand (sec)	9.24 (2.03)	9.98 (3.33)
MDHI total	18.7 (13.8)	26.5 (13.7)

BMI, body mass index; CASI, composite alternative splicing index; CTG, cytosine, thymine and guanine; MDHI, Myotonic Dystrophy Health Index; Q8W, every 8 weeks; QMT, quantitative muscle testing; SD, standard deviation; sec, seconds; vHOT, video hand opening time.

Favorable safety profile with no serious related TEAEs

Summary of treatment-emergent adverse events (TEAEs)¹

TEAE category	Participants with ≥1 TEAE – n (%)					Overall (N=56)
	1.8 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q4W+Rec. N=16	3.4 mg/kg Q8W N=8	5.4 mg/kg Q8W N=8	6.8 mg/kg Q8W N=8	
Any TEAE	16 (100)	16 (100)	8 (100)	8 (100)	8 (100)	56 (100)
Any related TEAE	9 (56)	9 (56)	2 (25)	3 (38)	6 (75)	29 (52)
Any serious TEAE	4 (25)	0	1 (13)	0	0	5 (9)
Any serious related TEAE	0	0	0	0	0	0
Any TEAE leading to withdrawal from study	0	0	0	0	0	0
Any TEAE leading to death	0	0	0	0	0	0

Most TEAEs were mild or moderate in intensity¹

- **6 serious TEAEs unrelated to study drug**
 - Atrioventricular block first degree (1)²
 - Pneumonia (2 events in same participant)
 - Pulmonary embolism (1)³
 - Hyponatremia (1)
 - Influenza (1)
- **Most common TEAEs (≥20% participant incidence)⁴**
 - Nasopharyngitis (38%)
 - Procedural pain (30%)
 - Influenza (27%)
 - Infusion-related reaction (25%)
 - Diarrhea; headache (each 21%)

Additional safety data

- **Liver enzyme elevations have been observed in a minority of participants**
 - No impact on liver function (bilirubin or coagulation)
 - Interpretation is complicated by underlying disease and elevated baseline values up to ~2.5x greater than the upper limit of normal
- **No participants have demonstrated persistent related anemia or thrombocytopenia**

~855 doses administered to date representing over 72 patient-years of follow-up¹

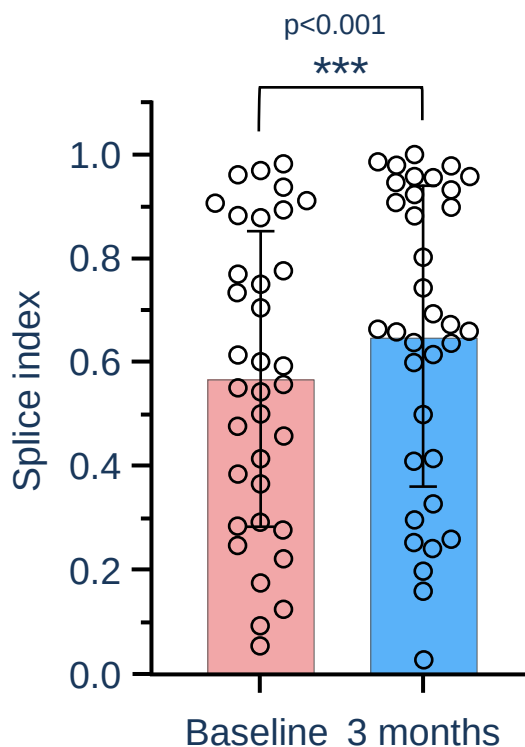
Q4W, every 4 weeks; Q8W, every 8 weeks; TEAE, treatment-emergent adverse event.

1. Data as of December 6, 2024; 2. Transient worsening of atrioventricular (AV) block in a participant with ongoing medical history of first-degree AV block;

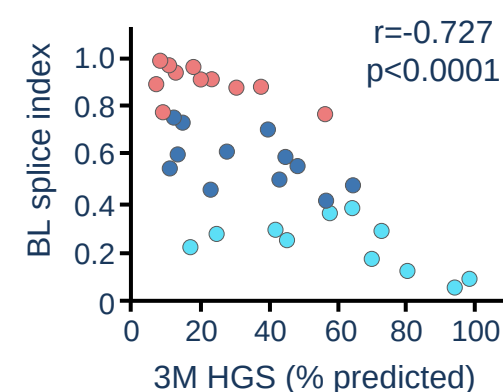
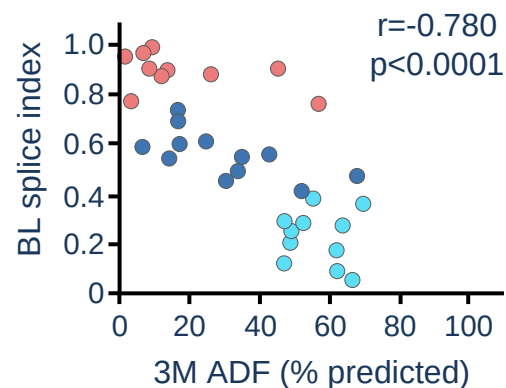
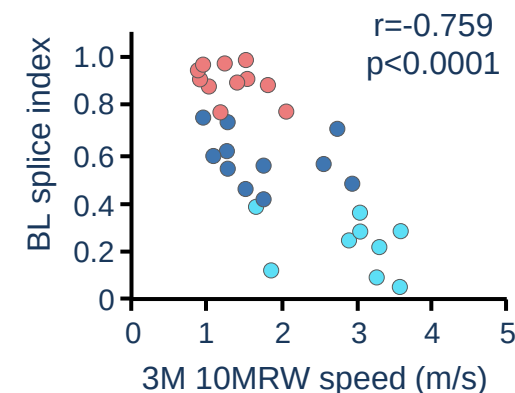
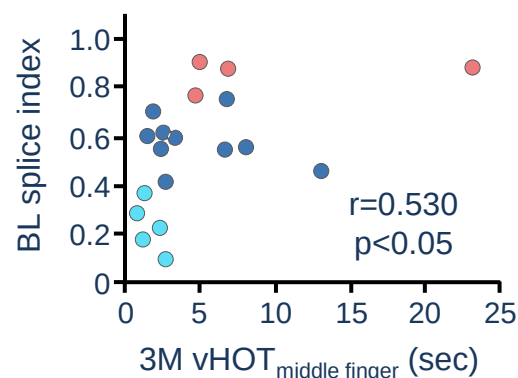
3. Attributed to risk factors for pulmonary embolism; 4. All cohorts combined; preferred terms are reported.

The Splice Index quantifies RNA splicing and is a prognostic biomarker that predicts clinical benefit in DM1

Worsening in Splice Index is observed in as little as 3 months in the NH cohort (N=35)*



The Splice Index is predictive of function



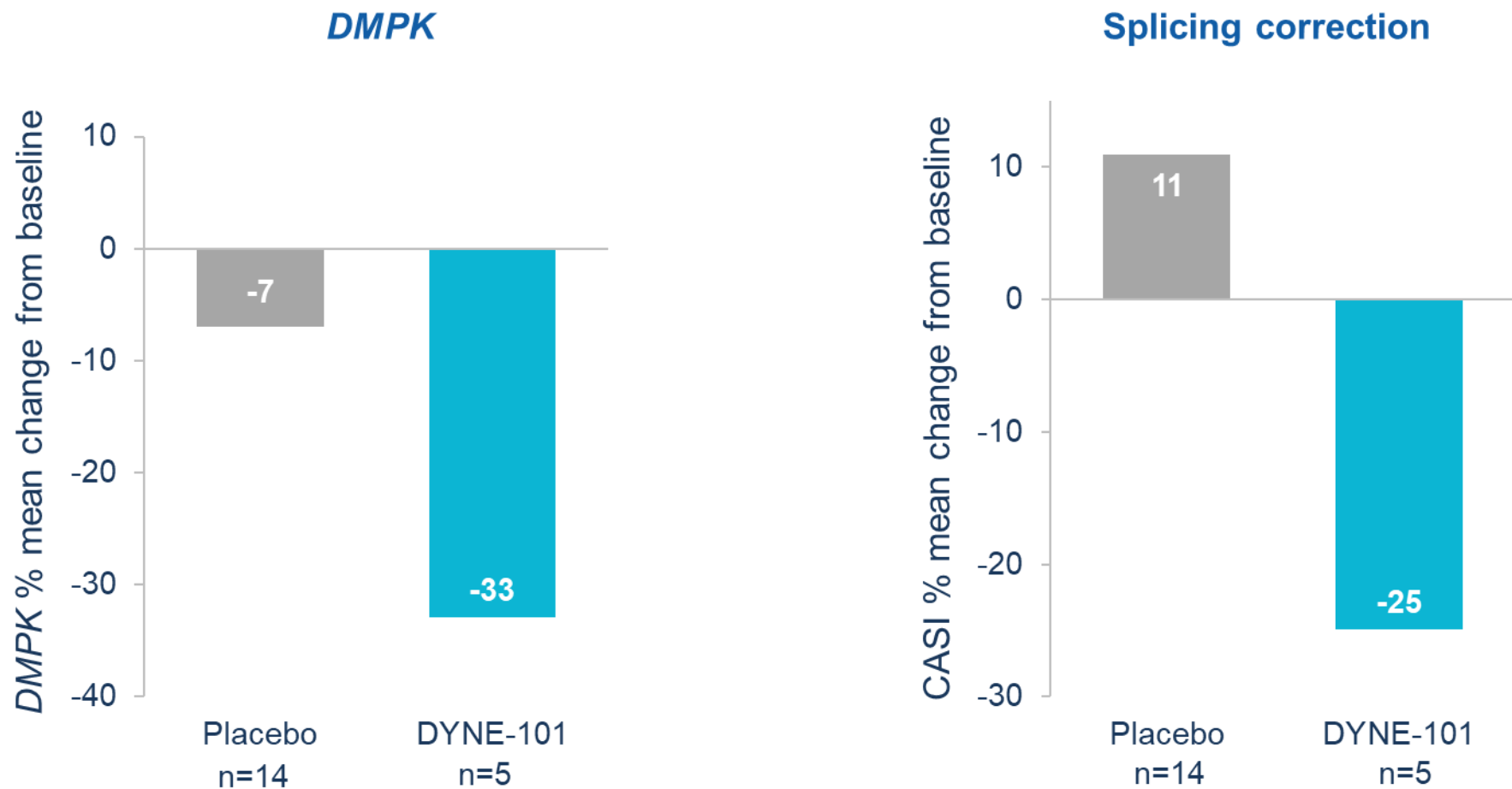
Splice Index group: ● Mild ● Moderate ● Severe

*Data represent mean $\pm$ standard deviation.

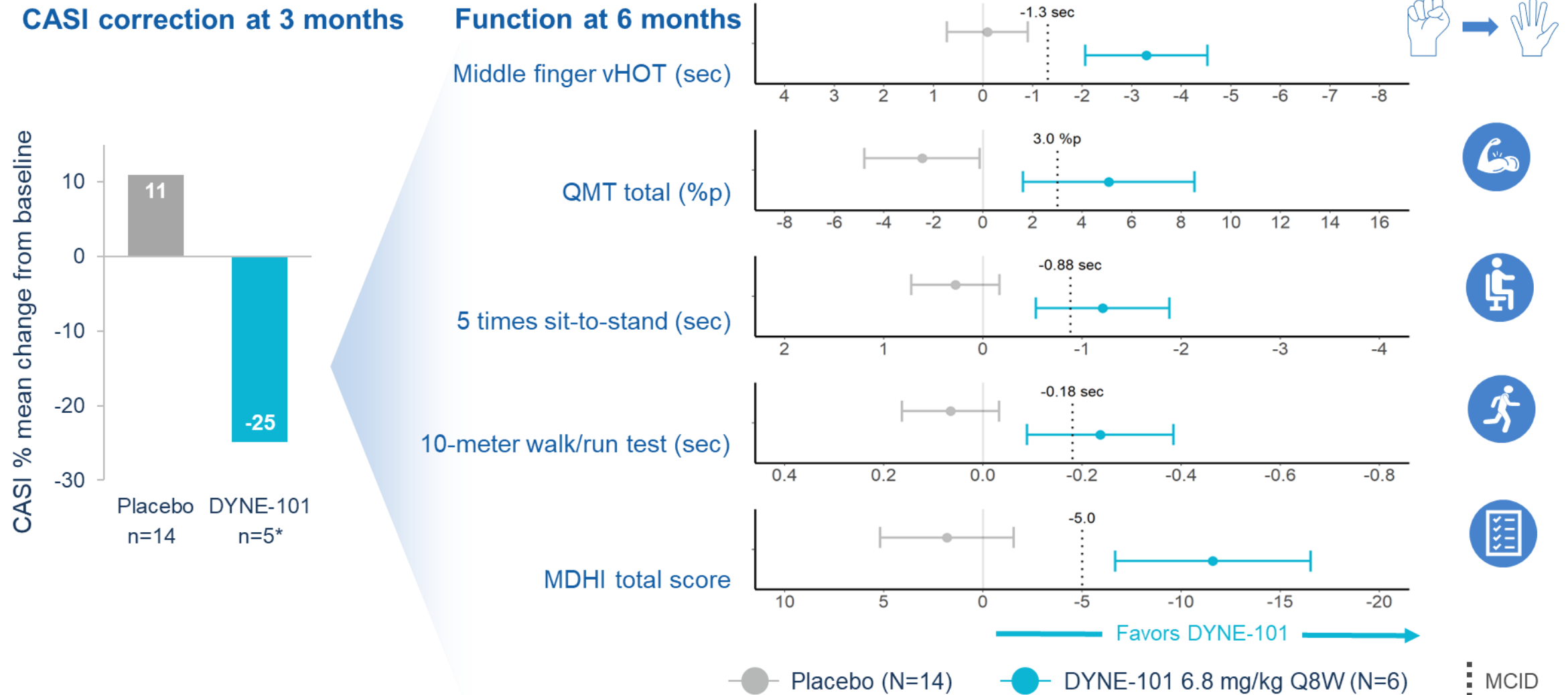
3M, 3 month; 10MRW, 10-meter walk/run; ADF, ankle dorsiflexion; BL, baseline; DM1, myotonic dystrophy type 1; HGS, hand grip strength; NH, natural history; vHOT, video hand opening time.

Provenzano M, et al. *J Clin Invest.* 2025:e185426.

DYNE-101 at 6.8 mg/kg Q8W improved the foundational pathobiology of DM1 at 3 months



DYNE-101 demonstrates functional improvement in areas that are most impactful for patients¹

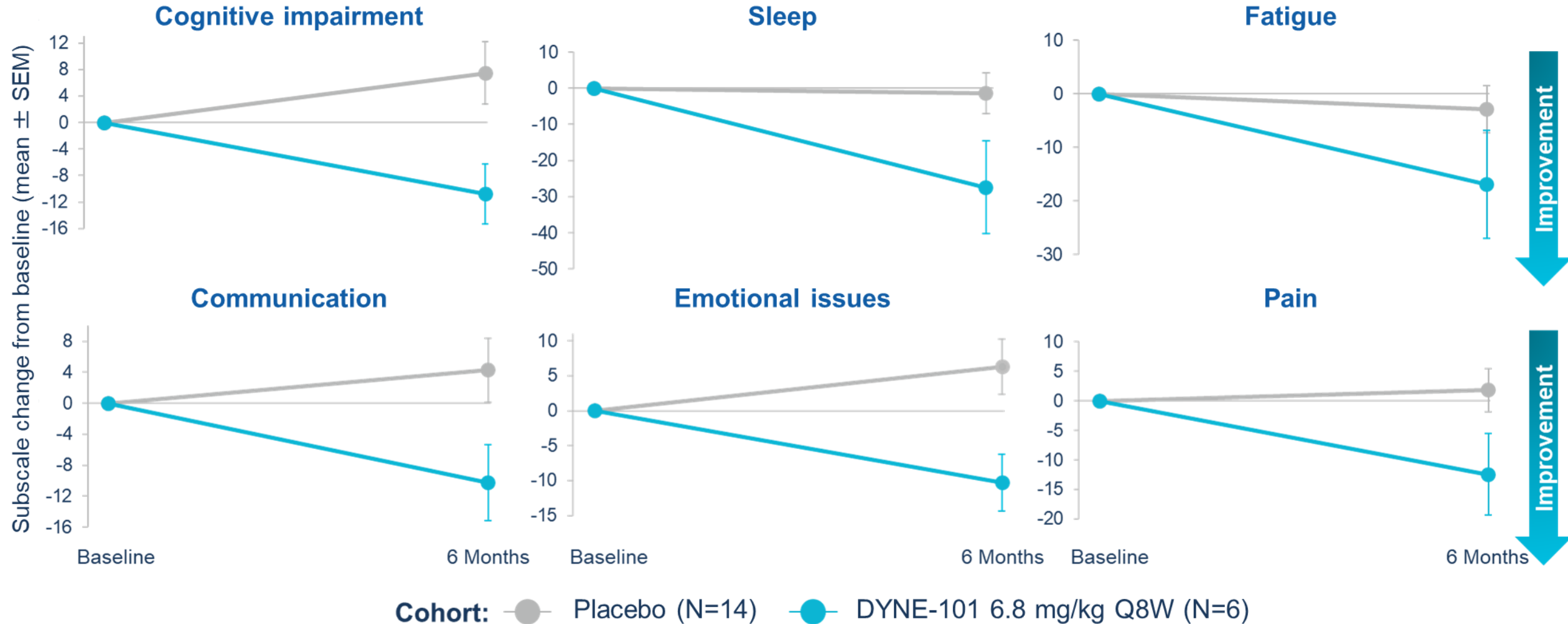


*One baseline sample in 6.8 mg/kg treatment group not included within splicing assay as the sample did not meet quality control criteria.

Mixed model for repeated measures (MMRM): fixed effects: dose, visit, baseline, dose by visit interaction, baseline by visit interaction. Data: all dose groups except recovery group; excluding placebo data after 6 months; Data presented are least squares (LS) mean change from baseline $\pm$ SE. MCID estimate is calculated as the average of 2 distribution-based methods using ACHIEVE data (0.2 SD of baseline [N=56] and 0.5 SD placebo change from baseline at 6 months [n=14]). 3 months = 85 days; 6 months = 169 days.

Q8W, every 8 weeks; CASI, composite alternative splicing index; CNS, central nervous system; MCID, minimal clinically important difference; MDHI, Myotonic Dystrophy Health Index; QMT, quantitative muscle testing; SD, standard deviation; SE, standard error; vHOT, video hand opening time. 1. Hagerman KA, et al. *Muscle Nerve* 2019;59(4):457-64.

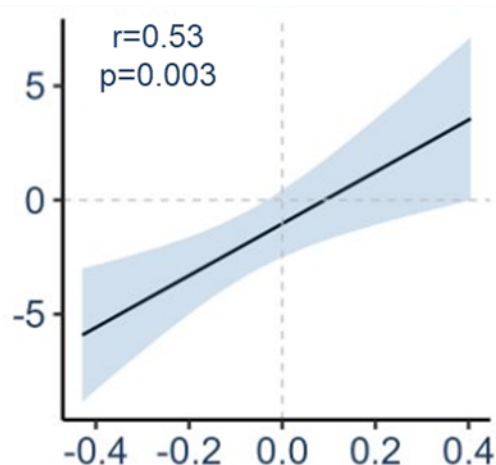
Improvement in CNS-related MDHI subscales



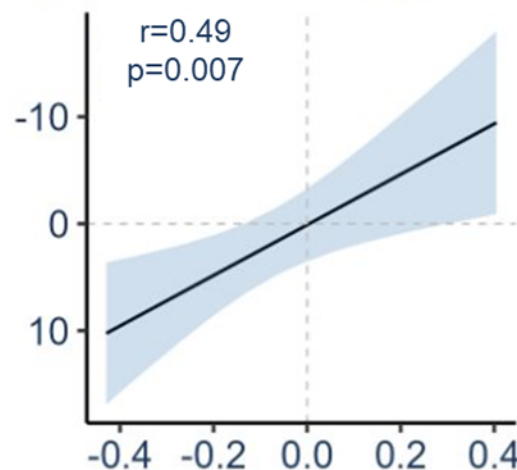
In ACHIEVE, splicing correction at 3 months predicted functional improvement at 6 months

Function change from baseline at Month 6

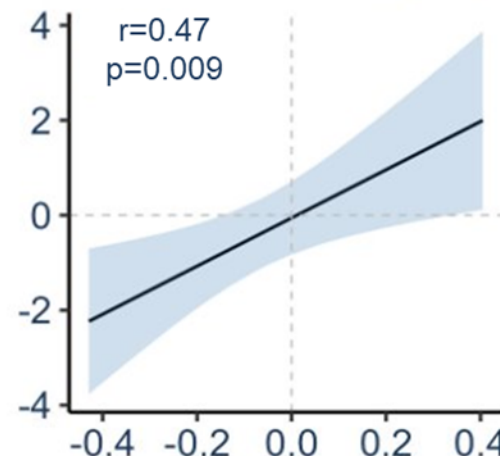
vHOT middle finger average (sec)



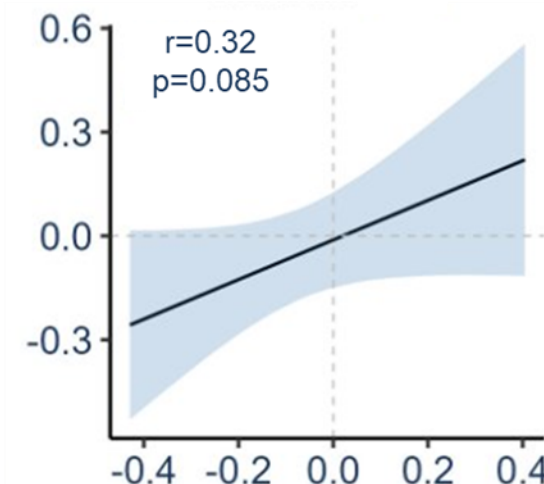
QMT total (%p)



5 times sit-to-stand (sec)



10-meter walk/run (sec)



CASI change from baseline at 3 months

Shown are linear regression lines and correlation analysis for pooled 3.4 mg/kg Q4W, 5.4 mg/kg Q8W and 6.8 mg/kg Q8W and Placebo (N=24). Band for model predicted mean with 95% CI.

3 months = 85 days; 6 months = 169 days.

CASI, composite alternative splicing index; Q4W, every 4 weeks; Q8W, every 8 weeks; QMT, quantitative muscle testing; sec, seconds; vHOT, video hand opening time.

Summary

- DYNE-101 is designed to target mutant nuclear *DMPK* RNA with the goal of correcting the abnormal splicing and enabling functional improvement in DM1^{1,2}
- DYNE-101 shows a continued favorable safety profile*, with no serious related TEAEs
- DYNE-101 addresses the underlying pathobiology (dysregulated splicing) of DM1 and at 6.8 mg/kg Q8W has demonstrated clinically meaningful functional improvement on measures of strength, mobility and quality of life, including CNS manifestations
 - Splicing correction at 3 months with DYNE-101 was predictive of functional improvement at 6 months
- The MAD portion of ACHIEVE is completed; 6.8 mg/kg Q8W has been selected as the registrational dose/dose regimen of DYNE-101

*Data as of December 6, 2024.

CNS, central nervous system; MAD, multiple ascending dose; Q8W, every 8 weeks; TEAE, treatment-emergent adverse event.

1. López-Martínez A, et al. *Genes (Basel)*. 2020;11(9):1109; 2. Zanotti S. Presentation at the 26th American Society of Gene and Cell Therapy Annual Meeting. May 17, 2023. Los Angeles, USA. Abstract 82.

Acknowledgements



ACHIEVE participants and their families

